REMARKS

Status of the Claims

Claims 23, 28-30, 36 and 50-89 are in the application.

Claims 23, 28-30, 36 and 50-89 have been rejected.

Claims 23, 28-30, 36 and 50-89 remain pending.

Applicants respectfully request reconsideration of the rejections and allowance of the claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 23, 28-30, 36, and 50-89 have been rejected under 35 U.S.C: §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office alleges that the claims are indefinite because the term "a therapeutically effective amount of pharmaceutical composition or conjugated compound that comprise an ST receptor ligand wherein said ST receptor ligand is an antibody, Fab or $F(AB)_2$" in claims 23, 63, and 81 is not clear. The Office alleges that although the term "therapeutically effective amount" is defined in the specification the term is still unclear because it fails to "teach what has been achieved in the treatment or whether the amount of the antibody used in the treatment is [a] 'therapeutically effective amount.'" (Office Action, page 3). Applicant respectfully disagrees.

The claims make clear the meaning of "a therapeutically effective amount." Claim 23 refers to "[a] method of treating an individual suspected of suffering from metastatic colorectal cancer…" Claims 63 and 81 each refer to "[a] method of treating an individual from metastatic colorectal cancer…" In each of claims 23, 63 and 81, the claim recites that the active agent "causes cell death, inhibits cell division or induces differentiation".

The specification provides further evidence of the clear meaning of "a therapeutically effective amount." Page 12, lines 10-23 of the specification states:

> One having ordinary skill in the art can readily identify individuals suspected of suffering from colorectal cancer and metastasized colorectal cells. In those individuals diagnosed with colorectal cancer, it is standard therapy to suspect metastasis and aggressively attempt to eradicate metastasized cells. The present invention provides pharmaceutical compositions and methods for imaging and thereby will more definitively diagnose metastasis. Further, the present invention provides pharmaceutical compositions comprising therapeutic agents and methods for specifically targeting and eliminating metastasized colorectal cancer cells. Further, the present invention provides pharmaceutical compositions that comprise therapeutics and methods for specifically eliminating colorectal cancer cells.

Page 37, lines 25-30 of the specification states:

> The pharmaceutical composition contains a therapeutically effective amount of the conjugated composition. A therapeutically effective amount is an amount which is effective to cause a cytotoxic or cytostatic effect on metastasized colorectal cancer cells without causing lethal side effects on the individual.

The term "therapeutically effective amount" as used in the claims is definite because one of skill in the art would understand that in light of the claims and the specification what the term means. In contrast to the clear meaning of the terms in the present application where the term is associated with a function to be achieved, the courts have held the term to be indefinite in those situation when, unlike the instant application, "the claim fails to state the function which is to be achieved and more than one effect can be implied from the specification or the relevant art." (M.P.E.P. 2173.05(c), citing *In re Fredericksen* 213 F.2d 547, 102 USPQ 35 (CCPA 1954)). Here, the function to be achieved is to eliminate metastasized colorectal cancer cells by cytotoxic or cytostatic effect, without lethal side effects. Unlike the situation where the term is indefinite, there is not more than one effect that can be implied from the specification or the

relevant art. The Office has not stated that there is no function associated with the term. In contrast, the Office quotes the definition of the term in the rejection where the function is clearly stated. Additionally, the Office has also not stated that there is more than one effect that could be associated with the term "therapeutically effective amount" when the term is read in light of the specification and the claims.

One of skill in the art would understand the meaning of the term to include any amount that that can cause the elimination of metastasized colorectal cancer cells by cytotoxic or cytostatic effect on a metastatic colorectal cancer cell without lethal side effects on the individual. The cytotoxic or cytostatic effect is the function that has been achieved by the treatment and one of ordinary skill in the art would understand the meaning of the term.

Accordingly, because the term "therapeutically effective amount" is associated with a function to be achieved the claims are definite. In view of the foregoing, Applicant respectfully requests that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claims 23, 28-30, 36, and 50-89 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The c1aims allegedly contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office alleges that "the specification invites the skilled artisan to experiment to determine how to use the claimed composition comprising an ST receptor antibody or the Fab or $F(ab)_2$ to treat metastatic colorectal cancer [but] does not set forth sufficient teachings to allow one skilled in the art to practice treating such cancer" without undue experimentation. (Office Action, page 4.) The Office alleges that the specification does not disclose information about the ST receptor being expressed in colorectal cancer cells; an antibody to the ST receptor interacting with the ST receptor on a colorectal cancer cell; or a method of treating any cancer with the composition comprising antibody to the ST. (Office Action, page 4.) The Office alleges that

undue experimentation is required because of these deficiencies and, for example, because the specification lacks working examples and lacks exactly "what the [ST] receptor is." (Office Action, page 4.) The Office also alleges that treating tumors with antibodies is unpredictable and that such unpredictability would also require one of skill in the art to use undue experimentation to practice the claimed invention. (Office Action, page 4.) Applicant respectfully disagrees.

The claims are enabled because the combination of the specification and the knowledge of one of skill in the art, to practice the claims would only require routine experimentation, not undue experimentation. The pending claims are directed to methods of treating metastatic colorectal cancer cells, i.e. causing the cells to stop growing or to kill them without causing lethal side effects in the individual. These methods are employed by using the expression of the ST receptor on the colon cancer cells as a target for the binding moiety or antibody, Fab, or Fab_2. The ability of the ST receptor to be used as the target allows for greater specificity in treatment without the unwanted side effects of non-specific cancer treatments, such as traditional chemotherapeutics that affect every cell not just a sub-class of cells. The present application identified that an important target that can be used for treating metastatic colon cancer is the ST receptor. The claims and specification do not recite in generic terms targeting metastatic colon cancer cells because such a generic claim would not be enabled because such a generic disclosure would not tell one of skill in the art how to target the metastatic colon cancer cell. In contrast, the present application and the claims specifically state that the cells are targeted because of the presence of the ST receptor. Armed with this knowledge one of skill in the art would be able to practice the claimed methods without undue experimentation.

The Official action refers to Jain (1994) as setting forth barriers to drug delivery to solid tumors. Jain does not stand for the proposition that drugs, including large molecules, cannot be effectively delivered to solid tumors. Clearly, while Jain reports the challenges that are involved in improving cancer therapies, it is well settled that drugs, including antibodies, can be effectively delivered to solid tumors. Dillman (1989) and Weiner (1999) support a finding of enablement in that it is acknowledged that while improvements are needed for more effective treatments, the technology was sufficient to provide some benefit. Dillman (1994) indicates that

at that time there were no unconjugated antibodies to have proven therapeutic benefit. In fact, unconjugated antibodies are known to have therapeutic benefit. (See Applicants Amendment filed July 7, 2004).

"The question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *Chiron v. Genentech*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). Additionally, the specification is not required to "describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *Id.* at 1253. The Federal Circuit has repeatedly stated that "a patentee preferably omits from the disclosure any routine technology that is well known at the time of application." *Id.* at 1254.

In *Chiron* the question was whether the application enabled humanized antibodies because the claim recited the term "chimeric antibodies." The court held that the specification did not enable one of skill in the art to make and use humanized antibodies because it was a nascent technology and a nascent technology requires a more complete disclosure "because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction." *Id.* at 1254. The record in *Chiron* showed that only a few laboratories had the necessary knowledge and necessary equipment to make humanized antibodies, and, therefore, at the time Chiron's application was filed one of skill in the art would have required undue experimentation to make humanized antibodies based on Chiron's application. *Id.*

Here, the technology of targeting cancer cells based on a receptor that is expressed on the cell surface was not nascent technology at the time the application was filed. For example, there are numerous examples of tumor cells, specifically metastatic colon cancer cells being treated using antibodies or similar molecules.

For example in Takahashi *et al.* (Thoku J. Exp. Med., Vol. 168, pp. 371-374 (1992), entitled "Monoclonal Antibody-Drug Conjugate Therapy for the Patients with Colorectal

Cancer") the authors demonstrated that antibodies raised against colon cancer cells that are conjugated with a drug (neocarzinostatin) were able to provide pain relief and decrease colon cancer metastasis in patients treated with the conjugate. Takahashi at 371. The decrease in metastasis would be within the definition of "therapeutically effective" for the pending claims. The survival rates of these patients were also slightly better. The Takahashi paper further states that such results were obtained even where HAMA was detected. Here, as in Takahashi, the tumor cells are being targeted indicating that nothing more than routine experimentation would be required to practice the present invention.

Furthermore, in Meredith *et al.* (*The Journal of Nuclear Medicine*, Vol. 33, pp. 1648-1653 (1992), entitled "Dose Fractionation of Radiolabled Antibodies in Patients with Metastatic Colon Cancer"), the authors demonstrated that administering to patients an antibody that can bind to cancer cells that is conjugated with radioactive iodine can either have a cytotoxic or cytostatic effect on the cancer.

Additionally in Debinski *et al.* (*Cancer Research*, Vol. 52, pp. 5379-5385 (1992), entitled "Monovalent Immunotoxin Containing Truncated From of Psuedomonas Exotoxin as Potent Antitumor Agent") the authors showed that an antibody to the transferrin receptor conjugated with the toxin was a potent antitumor agent in mice. *Id.* at 5382-83.

Therefore, these examples demonstrate that one of skill in the art had the knowledge at the time the application was filed to administer an antibody conjugated to an agent to a patient to treat cancer and specifically metastatic colon cancer as evidenced by these papers. The present application and pending claims provide a new target, the ST receptor, for the antibody or other types of binding moieties that can be used to target the cancer cells. "The specification need only teach those aspects of the invention that one skilled in the art could not figure out without undue experimentation. *See, e.g., Nat'l Recovery Techs.,* 166 F.3d at 1196 ('The scope of enablement ... is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation.')." *Warner Lambert v. Teva*, 418 F.3d 1326, 1337 (Fed. Cir. 2005). The present application teaches the novel and non-obvious use of the ST receptor to target metastatic colon cancer cells, which is the "aspect of the invention that

one of skilled in the art could not figure out without undue experimentation." The application need not teach the general methods of administering a composition as claimed because that is something one of skill in the art could already "figure out" without undue experimentation. Some experimentation is allowed so long as it is not undue. *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404. Therefore, one of skill in the art would not require undue experimentation to practice the claimed invention.

Additionally, the Office alleges that the pending claims are not enabled because the Applicant has not provided detailed information regarding the sequence of the ST receptor. As discussed above, the enablement requirement does not require the Applicant to supply information that is well known to one of skill in the art. "A patent need not teach, and preferably omits, what is well known in the art." *Falkner v. Inglis*, 448 F.3d 1357,1365 (Fed. Cir. 2006). (citing *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524, 1534 (Fed.Cir.1987)). Here, the ST receptor had been characterized at the time the present application was filed. In de Sauvage *et al.*, (*The Journal of Biological Chemistry*, Vol. 267, pp. 6479-6482 (1992), entitled: "Characterization of the Recombinant Human Receptor for Escherichia coli Heat-stable Enterotoxin"), the ST receptor was isolated and characterized after it had been cloned and sequenced in another article by the same group (*See*, .de Sauvage *et al.*, *The Journal of Biological* Chemistry, Vol. 266, pp. 17912-8 (1992), entitled: "Primary structure and functional expression of the human receptor for Escherichia coli heat-stable enterotoxin). Similarly, Currie, M. G. et al. (1992) Proc. Natl. Acad Sci. USA 89:947-951, which was incorporated in the specification by reference on page 14, lines 13-15, disclose that ST receptors were known as receptors which bind to heat stable enterotoxin ST. Currie refers to reference 5 which reports the cloning of the receptor. From the cloning, isolation, and characterization results reported by Currie and the two papers authored by de Sauvage *et al.*, it is clear that the identity of the protein referred to in the specification as the "ST receptor" was known to one of skill in the art at the time the invention was made and that those skilled in the art would only need routine experimentation to raise antibodies or develop other binding partners against the protein. At the time the a-pplication was filed, the identity of the intestinal protein which binds to heat stable

enterotoxin was well established; the ST-receptor was known to be a specific and identifiable protein. Therefore, because the ST-receptor was well known in the art at the time the present application was filed, one of skill in the art would not need to use undue experimentation to practice the claimed.

Furthermore, Applicants respectfully assert that the evidence relied upon by the Office does not support the conclusion that the present invention is not enabled. As Applicant stated in the previous response (dated August 23, 2006) the references cited by the Office do not contradict or cause one of skill in the art to doubt Applicant's claim that the present invention is enabled. The Office has still failed to present sufficient evidence why one of skill in the art would doubt the objective truth of Applicant's assertion of enablement. Additionally, in view of the references cited above that indicate that similar methods using different targets work and are enabled one of skill in the art would not doubt Applicant's assertion that the claims are enabled. When all of the evidence is viewed in its totality one skilled in the art would accept the object truth of Applicant's assertion of enablement. The evidence of record supports a finding that the invention is enabled as required under the law. Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Double Patenting Rejections

Claims 23, 28-30, 36, and 50-89 remain and/or are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 10, 28\-31, and 54-58 of U.S. Patent No. 5,879,656.

Claims 23, 28-29, 58, 63-65, 76, 81, 82, and 85 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 6 and 8 of U.S. Patent No. 6,060,037 ('037) in view of de Sauvage et aI., (JBC, vol 267, page 6479-6482, April, 1992).

As noted in previous responses, once claims have been indicated to be allowable, Applicants shall promptly provide Terminal Disclaimer as appropriate. To that end, the

Examiner is invited to contact Applicants' undersigned representative and inform him of the allowability of the claims so that a Terminal Disclaimer can be promptly filed.

Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7855 if there are any questions regarding Applicants' claimed invention.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436.

Respectfully submitted,

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Attachments: Takahashi *et al.* (1992) *Thoku J. Exp. Med.,* 168:371-374
Meredith *et al.* (1992) *The Journal of Nuclear Medicine*, 33:1648-1653
Debinski *et al.* (1992) *Cancer Research*, 52:5379-5385
de Sauvage *et al.*, (1992) *The Journal of Biological Chemistry*, 267:6479-6482
de Sauvage *et al.*, (1992) *The Journal of Biological Chemistry*, 266:17912-8
Currie, M. G. et al. (1992) Proc. Natl. Acad Sci. USA 89:947-951